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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,601	08/24/2006	Sabine Balthasar	RO4304US (#90568)	8967

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EXAMINER	
WHEELER, THURMAN MICHAEL	
ART UNIT	PAPER NUMBER
1619	
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01/31/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,601	BALTHASAR ET AL.	
	Examiner	Art Unit	
	Thurman Wheeler	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 0201*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14 and 16-18* is/are pending in the application.

4a) Of the above claim(s) *6-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 5 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 4-14 and 16-18 are pending

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 09/07/2010 has been entered.

2. Claims 6-14, 17 and 18 are withdrawn.

3. Claim 1 has been amended.

4. Herein, claims 1, 2, 4, 5 and 16 are for further prosecution.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

> would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining differences between the prior art and claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.
> 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 5 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreuter et al ((WO 02089776) where USP 2004/0131692 is used as English equivalent of PCT/EP2002/004735. Citations are to the English equivalent document, of record) and Paganelli (EPO 049607, 1992) and Langer (European Journal of Pharmaceutics and Biopharmaceutics, 1999, IDS).

Applicants claimed invention is directed to a carrier system for the cell-specific, intracellular enrichment of at

least one pharmacologically active substance, wherein said carrier system is present in the form of protein-based nanoparticles to which biotinylated antibodies are bound, wherein said nanoparticles are based on at least one protein selected from the group consisting of gelatine and serum albumin, and said biotinylated antibodies are bound by forming a stable avidin-biotin complex with avidin which is covalently bound to the nanoparticles by bifunctional spacer molecules which are attached to reactive groups present on the surface of the nanoparticles; and wherein said antibodies enable a cell-specific attachment and cellular absorption of the nanoparticles.

Kreuter teaches nanoparticles comprising proteins, e.g. gelatine ([0009]; [0024], claim 2; claim 13; claim 23) and human serum albumin ([0001]; [0007-8]; [0023]; [0035]; claim 2; claim 13; claim 23) coupled with antibodies ([0012]; claim 5).

Kreuter teaches in a preferred embodiment, the inventive nanoparticles have covalently coupled avidin, via which biotinylated apolipoprotein E can be bound as is illustrated in FIG. 1. Avidin itself is a glycoprotein which is highly affine to biotin and is covalently bound via the aforementioned bifunctional spacer molecules to the thiol groups of the thiolated nanoparticles. By the covalent linkage of the avidin to the nanoparticles it is not only possible to bind biotinylated ApoE, which is necessary for the transport to the blood-brain barrier, but also to bind a variety of biotinylated molecules to the avidin-modified nanoparticles in a particularly

efficient manner. For this purpose, pharmacologically or biologically active molecules are especially preferred [0013].

Further, Kreuter teaches to impart pharmacologic effects, pharmacologically or biologically active substances are incorporated in the nanoparticles, or they are bound by the nanoparticles, where the binding of the active agents may be performed covalently, with complex-formation via the avidin-biotin system, as well as incorporatively or adsorptively ([0014]; claim 8; claim 9, claim 10).

Kreuter teaches amino groups, carboxyl groups, and hydroxyl groups located on the surface of the nanoparticles can be converted by suitable reagents to reactive thiol groups, where functional proteins are bound to the thiol group-modified nanoparticles via bifunctional spacer molecules having reactivity both to amino groups and free thiol groups [0011]. The functional proteins to be coupled to the nanoparticles are selected from the group comprising avidin, avidin derivatives, apolipoproteins such as apolipoprotein E, and also antibodies [0012].

However, the Kreuter reference does not explicitly embody using biotinylated monoclonal antibodies bound by a stable avidin-biotin complex.

Paganelli teaches a biotinylated monoclonal antibody, or

biotinylated fragments thereof, specific to a tumour-associated antigen expressed by the tumor, wherein a protein of the avidin type binds to biotin. Furthermore, Paganelli teaches a biotinylated monoclonal antibody is administered to a patient, such that avidin is and subsequently administered that specifically binds to the biotinylated monoclonal antibody (col.2, lns.15-32; col.4, lns.21-40).

Langer teaches the preparation of avidin-labeled protein nanoparticles as carriers for biotinylated peptide nucleic acid. Langer teaches preparing protein nanoparticles followed by covalent linkage of avidin, wherein free sulfhydryl groups were introduced onto the surface of protein nanoparticles. The number of primary amino groups and sulfhydryl groups on the surface of the resulting particles was quantified with site- specific reagents. Further, avidin was attached to the surface of the thiolated nanoparticles via a bifunctional spacer. Biotinylated peptide nucleic acid (PNA) was effectively coupled to the nanoparticles by complex formation with the covalently attached avidin (see Fig. 1).

It would have been obvious to one skilled in the art at the time of the invention to modify the nanoparticles as taught by Kreuter to include biotinylated monoclonal antibodies that are complexed with avidin, because Kreuter teaches that a variety of

biotinylated molecules can be complexed to the avidin-modified nanoparticles in an efficient manner. Furthermore, Paganelli explicitly teaches that a biotinylated monoclonal antibody can be complexed to a protein of the avidin type. One would have been motivated to provide a biotinylated monoclonal antibody, since it can be used to specifically target a tumour-associated antigen expressed by a tumor. Additionally, one skilled in the art would have recognized that other biotinylated molecules such as peptide nucleic acids could also be complexed to nanoparticles via an avidin complex as taught Langer. Thus, one skilled in the art would have recognized that a biotinylated monoclonal antibody could also be complexed to the nanoparticle as taught by Kreuter for purpose of targeting the nanoparticle to a tumor site.

One skilled in the art at the time of the invention would have had a reasonable expectation of success to provide a nanoparticle as claimed by Applicants by following the teachings of Kreuter, Paganelli and anger, as a whole.

Conclusions

6. Claims 1, 2, 4, 5 and 16 are rejected.

Applicants' Arguments

7. Applicants argue that Kreuter fails to teach nanoparticles having biotinylated antibodies bound to avidin moieties which are coupled to the nanoparticle surface via bifunctional spacer molecules.

Applicants' arguments filed 07 September 2010 have been fully considered but they are not persuasive in view of the new grounds of rejection, which describes why it would be prima facie obvious to modify the nanoparticles as taught by Kreuter in order to include biotinylated monoclonal antibody complexed via avidin to the nanoparticles.

8. Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thurman Wheeler whose telephone number is (571)270-1307. The examiner can normally be reached on 9:00 a.m.-5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached (571)272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635